Original Article

The minimum volume of pleural fluid required to diagnose malignant pleural effusion: A retrospective study

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ABSTRACT

Background: Pleural fluid cytology is a quick and accurate method to diagnose malignant pleural effusions. The optimal volume of fluid for cytological analysis has not yet been identified, and clinical recommendation based on some published clinical experiences has been to send large volumes of fluid for cytological analysis. A quality improvement initiative at our institution was conducted to determine the volume of fluid sufficient for a diagnosis of malignant pleural effusion. **Materials and Methods:** The study was approved by the Institutional Review Board. All pleural fluid specimens that were divided into three volumes (25 mL, 50 mL, and 150 mL) and sent for cytological examination were reviewed. **Results:** A total of 74 samples from 60 individual patients were evaluable. Thirty-six patients (60%) had a previous diagnosis of malignancy. Of the 74 specimens, 26 (35.1%) were positive for malignancy. The detection rate for malignant pleural effusion by cytology for 25 mL, 50 mL, and 150 mL were 88.5%, 96.2%, and 100.0%, respectively ($P = 0.16$). Two specimens that were negative in the 25 mL samples turned out to be positive in the 50 mL and 150 mL samples. One specimen was negative in the 25 mL and 50 mL samples but positive in the 150 mL sample. **Conclusions:** Our study did not show any statistically significant difference in the detection of malignant effusion in the 25 mL, 50 mL, and 150 mL group.

KEY WORDS: Cytology, malignant, pleural effusion

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INTRODUCTION

Pleural effusions are common clinical manifestations of benign and malignant diseases. The gold standard to diagnose malignant pleural effusion is to find malignant cells on cytological examination of pleural fluid or histopathology of pleural biopsy. Cytological analysis has sensitivity from 40% to 87% for malignant pleural effusion,[1-3] however, the optimal volume of fluid to be sent for cytological analysis is unclear, and only a few studies have addressed this issue.[4-7] In an attempt to address this question, we started to divide pleural fluid into three different volumes for cytological examination. We report our findings in this study.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board at Washington, DC, Veteran Affair Medical Center. An electronic cytology database was searched for all pleural fluid specimens sent for analysis between April 1, 2009, and July 31, 2015. The inclusion criteria included patients

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with suspected malignant pleural effusion in whom the pleural fluid was divided into three aliquots of 25 mL, 50 mL, and 150 mL. Patients with pleural effusion which was not suspected to be malignant or was not divided into the above three aliquots were excluded. The search identified 74 specimens which met the above criteria.

All specimens in the current study were processed according to standard clinical laboratory protocols. Specimens were either processed fresh or after refrigeration overnight without fixation. The 25 mL, 50 mL, and 150 mL specimens were transferred into 1, 2, or 3 50 mL centrifuge tubes, respectively. They were centrifuged for 5 min at 2500 revolutions per minutes. For 25 mL and 50 mL specimens, the direct smears and liquid-based preparations (ThinPrep™) were prepared from the sediment. Cell blocks were made from the remaining material. For the 150 mL specimens, direct smears, ThinPrep™ and cell blocks were performed from each of three centrifuge tubes, respectively. The direct smears were stained with Diff-Quik, ThinPrep™ was stained with Papanicolaou stain, and cell blocks were stained with Hematoxylin and Eosin.

Each specimen was categorized as either negative (no malignant cells or atypical cells) or positive (malignant cells). The specific cancer diagnoses were documented. The medical records were then searched, and any previous, or concurrent diagnosis of malignancy was documented. The chest images were reviewed.

Statistical analysis

The Chi-square tests were done to assess the relationship of demographics, past medical history information, and the malignancy diagnosis. Fisher's exact test was used to confirm the Chi-square tests results for small frequencies.

RESULTS

There were 74 samples from 60 individual patients, including 58 males and 2 females [Table 1]. The mean age of patients with a positive cytology was 70.6 years (range: 50–91 years, standard deviation [SD] 10.0 years), whereas the mean age of patients with a negative cytology was 69.9 years (range: 42–93 years, SD 11.6 years), $P = 0.41$. There was no difference in gender, race, and history of smoking between groups with positive or negative pleural fluid cytology. The final diagnosis results are shown in Table 2.

A total of 36 patients (60%) had a previous diagnosis of malignancy. The primary tumors comprised a heterogeneous group with the most common type being undifferentiated nonsmall cell lung cancer (19.4%), adenocarcinoma of the lung (16.7%), and squamous cell lung cancer (16.7%).

Of the 74 pleural fluid specimens, 26 (35.1%) were positive for malignancy [Table 3]. In seven patients, positive cytology was the first pathologic documentation of malignancy. Effusions in patients with a history of cancer did not have a higher rate of malignant effusions compared to patients without a history of cancer (41.5% vs. 37.9%; $P = 0.77$) [Table 4].

The cancer cell type with positive pleural fluid cytology in our study population is shown in Table 5. Lung adenocarcinoma was the most common cancer cell type and was diagnosed in 8 of 22 (36.4%) patients.

The results of the size of all the effusions on the chest radiographs before the thoracentesis are shown in Table 6, which correlate with the volume which was aspirated during the thoracentesis. The chest image findings of patients with malignant pleural effusion on cytology are shown in Table 7.

Table 1: Demographics of study patients

Variables	Number of patients	Number of patients with positive pleural fluid cytology	*P**
Gender			
Male	58	22	0.53
Female	2	0	
Race			
White	20	8	0.60
Black	37	14	
Other	3	0	
History of smoking			
Yes	53	21	0.25
No	7	1	
History of cancers			
Yes	36		-
No	24		

**P* values from Fisher's exact tests*

Table 2: Final diagnosis of the pleural effusions

Final diagnosis	Number of patients
Malignant	24
Nonmalignant	18
Without final diagnosis	18
Total	60

Table 3: Cytology results of all the pleural fluids

Cytology	Number of specimens
Malignant	26
Indeterminate or atypical	2
Benign	46
Total	74

Table 4: History of malignancies and the results of the pleural effusion

History of any malignancy	Number of specimens	Number of malignant pleural effusion on cytology* (%)	*P***
Yes	41	17 (41.5)	0.77
No	29	11 (37.9)	
Total	70	28 (40.0)	

*Only the specimens collected before any change of cancer treatment were included. (four specimens were excluded due to received chemotherapy before the thoracentesis), ** *P* values from Chi-square tests

The aspirated pleural fluid volumes ranged between 225 mL and 2095 mL with a median volume of 1175 mL. The detection rate for malignant pleural effusion by different volumes is shown in Table 8. One specimen with metastatic colon adenocarcinoma and the other with lung adenocarcinoma were negative in the 25 mL samples and positive in the 50 mL and 150 mL samples. One specimen with metastatic colon adenocarcinoma was negative in the 25 mL and 50 mL samples but positive in the 150 mL sample.

DISCUSSION

Patients with malignant effusion have advanced stage cancer and carry a poor prognosis. Cytological examination of pleural effusion is the most common method to confirm malignant pleural effusion. The diagnostic accuracy of pleural fluid cytology for a malignant effusion ranges from 40% to 87%, which is higher than that of pleural biopsy.[1,2]

There are no clear guidelines regarding the minimal volume of fluid needed to diagnose a malignant pleural effusion. Only a few studies have been published regarding the volume required to diagnose malignant pleural effusion. The American College of Physicians Health and Public Policy Committee stated in a position paper that only 50–100 mL of fluid is required for a diagnostic thoracentesis. However, the statement did not specifically address cytological examination for malignancy. The British Thoracic Society recommends that no more than 50 mL is required for adequate assessment.[8] Abouzgheib *et al*. divided the pleural effusion into first 50 mL and the rest.[4] They found that submission of >50 mL of pleural fluid did not increase diagnostic yield. Swiderek *et al*. divided the pleural fluid in 10 mL, 60 mL, and ≥150 mL.[5] Based on the study, 60 mL was found to be adequate for diagnosing a malignant pleural effusion. Thomas *et al*. found 25–50 mL of fluid was adequate to diagnose malignant pleural effusion.[6] The recent retrospective analysis of 2450 cases by Rooper *et al*. supports the use of 75 mL as a minimum cut-off volume for effusion specimen.[7]

In our study, there was no statistically significant difference in diagnosing malignant pleural effusion amongst the 25 mL, 50 mL, and 150 mL groups. Two specimens were negative in the 25 mL group, but positive in the 50 mL and 150 mL group. One specimen was negative in the 25 mL and 50 mL group, but positive in the 150 mL group.

There was no significant difference in the proportion of positive malignant pleural effusion in patients with a history of malignancy compared to those without a history of malignancy. Malignant effusion was the first presentation of new cancer in seven of our patients.

The mechanism by which pleural effusion develops in a patient with malignancy is one of the determinants for the presence or absence of malignant cells in the fluid. Pleural effusions that form due to the presence of tumor implants on pleural surface or due to direct tumor infiltration of the pleura tend to have malignant cells in the effusion. Pleural effusions can also occur due to the impairment of lymphatic drainage of the pleura either due to tumor infiltration of the lymph nodes or increased resistance to lymph flow into the vascular system. These are called paramalignant effusions[9] and malignant cells are not present in these effusions.

Another factor could be the histologic type of the underlying tumor which may affect the incidence of positive malignant cells in the pleural effusion. In our study, primary adenocarcinoma of lung and nonlung primarily accounts for 59.1% of the malignant pleural effusions. It could be that these tumors are more likely to have lymphohematogenous invasion with spread to pleural surface.

Table 5: Cancer cell type for all patients with positive cytology

Cell type	Number of patients
Lung carcinoma	
Adenocarcinoma	8
Undifferentiated nonsmall cell lung cancer	3
Small cell carcinoma	3
Metastatic carcinoma of nonlung primary	
Adenocarcinoma	5
Other cell type	1
Leukemia	2
Total	22

Table 6: Size of the pleural effusion on the chest radiographs*

Size	Number of specimens
Small	15
Moderate	19
Large	40

*The size of the pleural effusion was estimated on upright chest X-ray. Small: The meniscus obscured the hemidiaphragm, Moderate: The fluid occupied the lower 1/3 of the hemithorax, Large: The fluid occupied above the lower 1/3 of the hemithorax

Table 7: Chest radiographic finding of the specimens with malignant pleural effusion on cytology

Chest radiographic finding	Number of specimens
Size of the pleural fluid	
Small	4
Moderate	3
Large	19
Hilar and/or mediastinum lymphadenopathy	26
Parenchymal involvement	26
Infiltration	13
Emphysema	5

Table 8: Pleural fluid volume and malignancy diagnosis*

Volume (mL)	Number of specimens with positive malignant cells	Detection rate (%)	*P*
25	23	88.5	0.16
50	25	96.2	
150	26	100.0	

*26 specimens were diagnosed with malignant pleural fluid by cytology

Although the results from our study and that by Thomas *et al*.[6] would suggest that 25–50 mL of pleural fluid would be adequate to diagnose malignant pleural effusion and that there were no statistical differences in the diagnostic rate between the three groups in our study, these differences may be clinically relevant. Rooper *et al*. found that using a volume cut-off of 75 mL is no different from using any greater volume cut-offs, however, definitively benign or malignant effusion cytology results are more likely to come from high-volume specimens above the adequacy threshold of 75 mL.[7] In our opinion, the least amount of volume of pleural fluid that should be processed for cytological examination should be 25 mL and the largest volume that should be submitted should be largest volume that a laboratory can process at one time, without adding significant monetary or time-related cost.

There are several limitations to our study. The sample size and the number of patients with a malignant effusion are small. Majority of the patients in our study were male, and the results may not be applicable in centers with more female patients. We did not evaluate pleural fluid volume larger than 150 mL; hence, we are unable to say if volumes larger than 150 mL add to the diagnostic accuracy of malignant effusions.

CONCLUSIONS

Our study did not show any difference in the detection of malignant effusion in the 25 mL, 50 mL, and 150 mL groups.

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Conflicts of interest
There are no conflicts of interest.

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